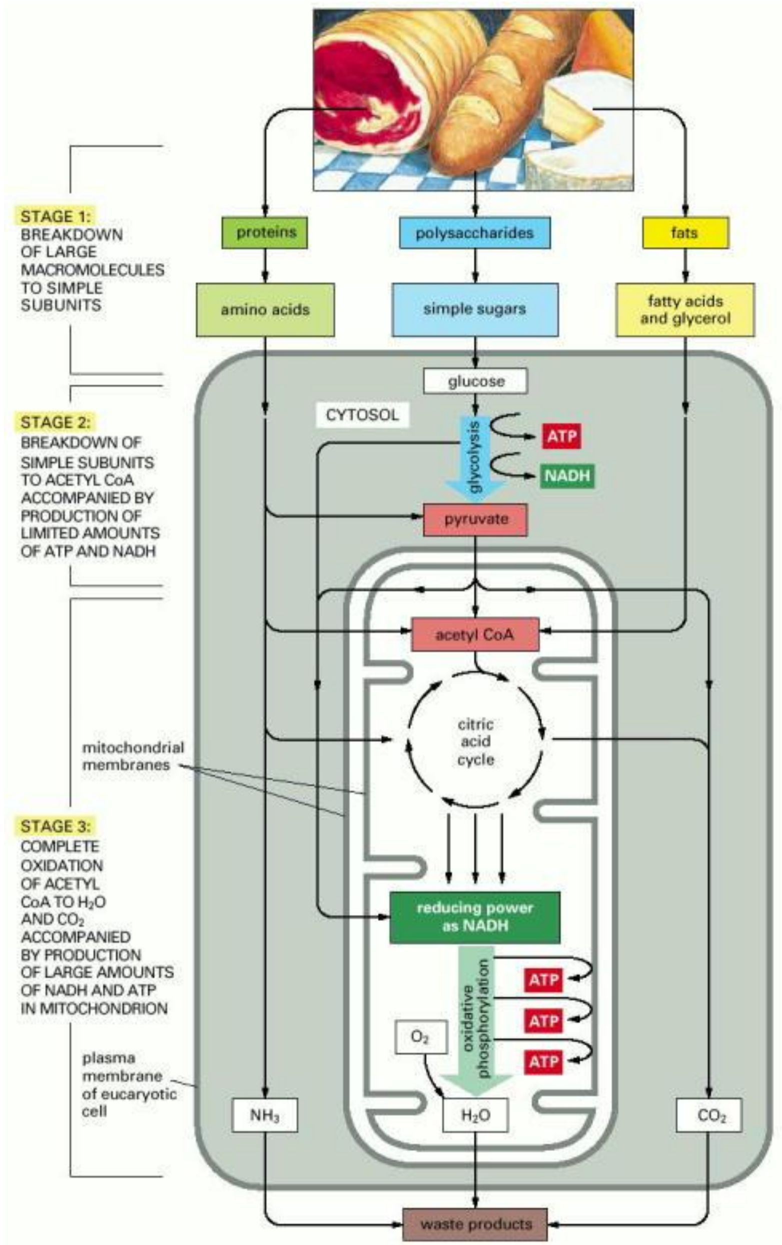
Fat metabolism



Common food composition:

- **carbohydrates: 45-50%**
- **fats: 35-40%**
- **proteins: 10-15%**

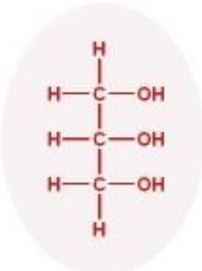
Fats: compounds can be solved in apolar solvents

Average daily fat consumption: 50-150 g

- **90% tryglycerides**
- **remaing**: cholesterin, cholesterin-esthers, phospholypids, fatty acids

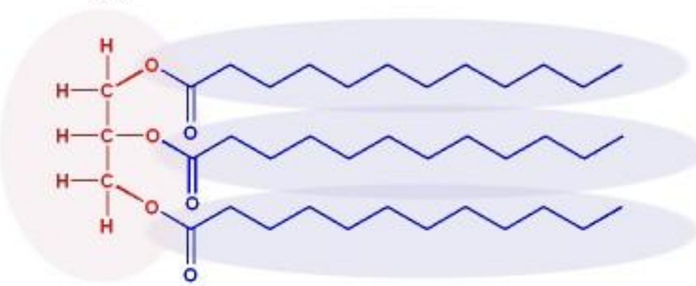
tryglycerides

Glycerol

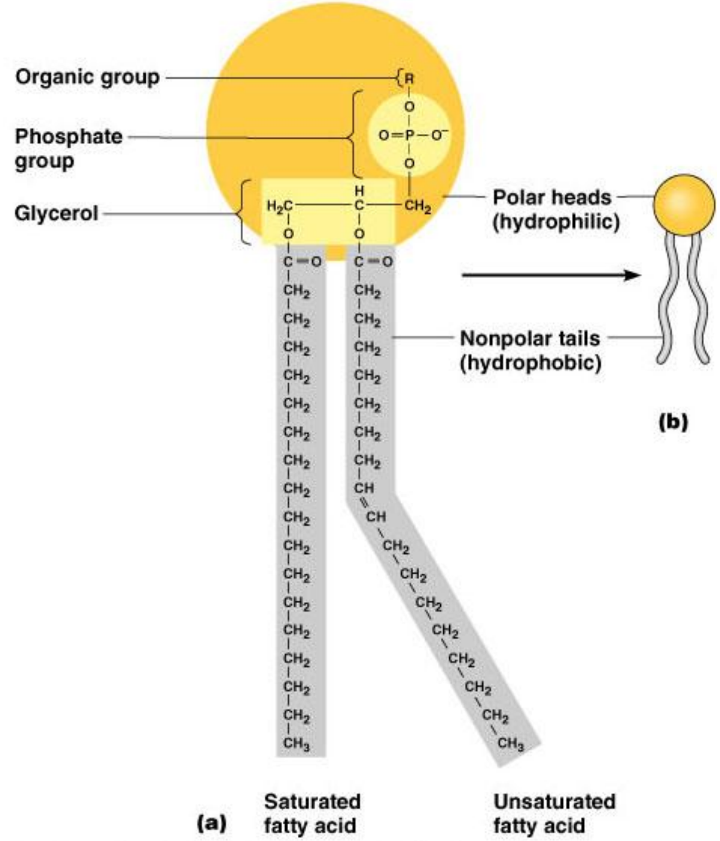


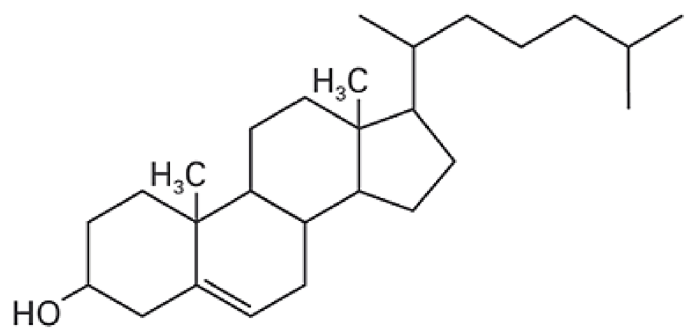
A "free" Fatty Acid

Triglyceride



phospholypids

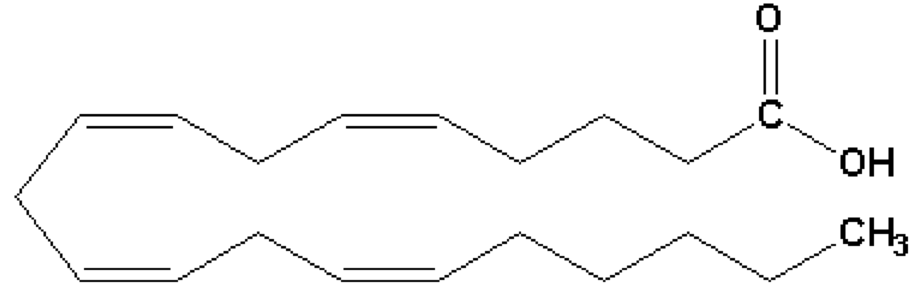




Cholesterin

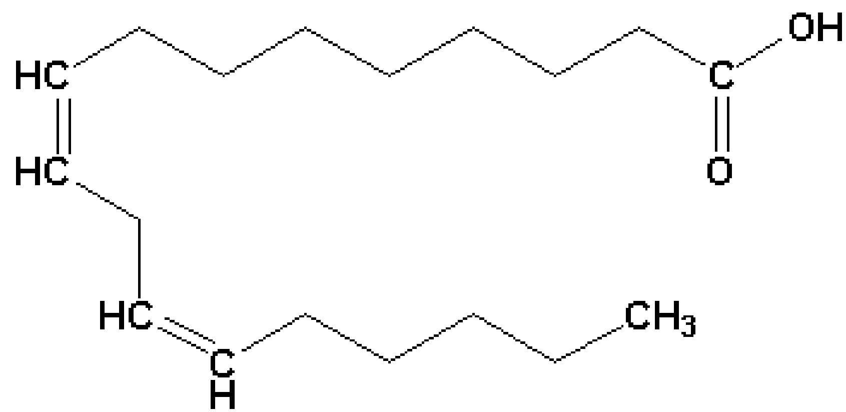
Fatty acids

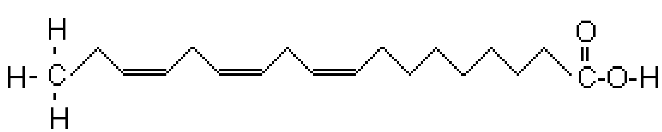
Zsírsav neve	C-atomok száma	Kettős kötések száma	Kettős kötések helyzete	
palmitinsav	16	0		
palmitoleinsav	16	1	Δ9	ω-7
sztearinsav	18	0		
olajsav	18	1	Δ9	ω-9
linolsav	18	2	Δ9, 12	ω-6
linolénsav	18	3	Δ9, 12, 15	ω-3
arachidonsav	20	4	Δ5, 8, 11, 14	ω-6

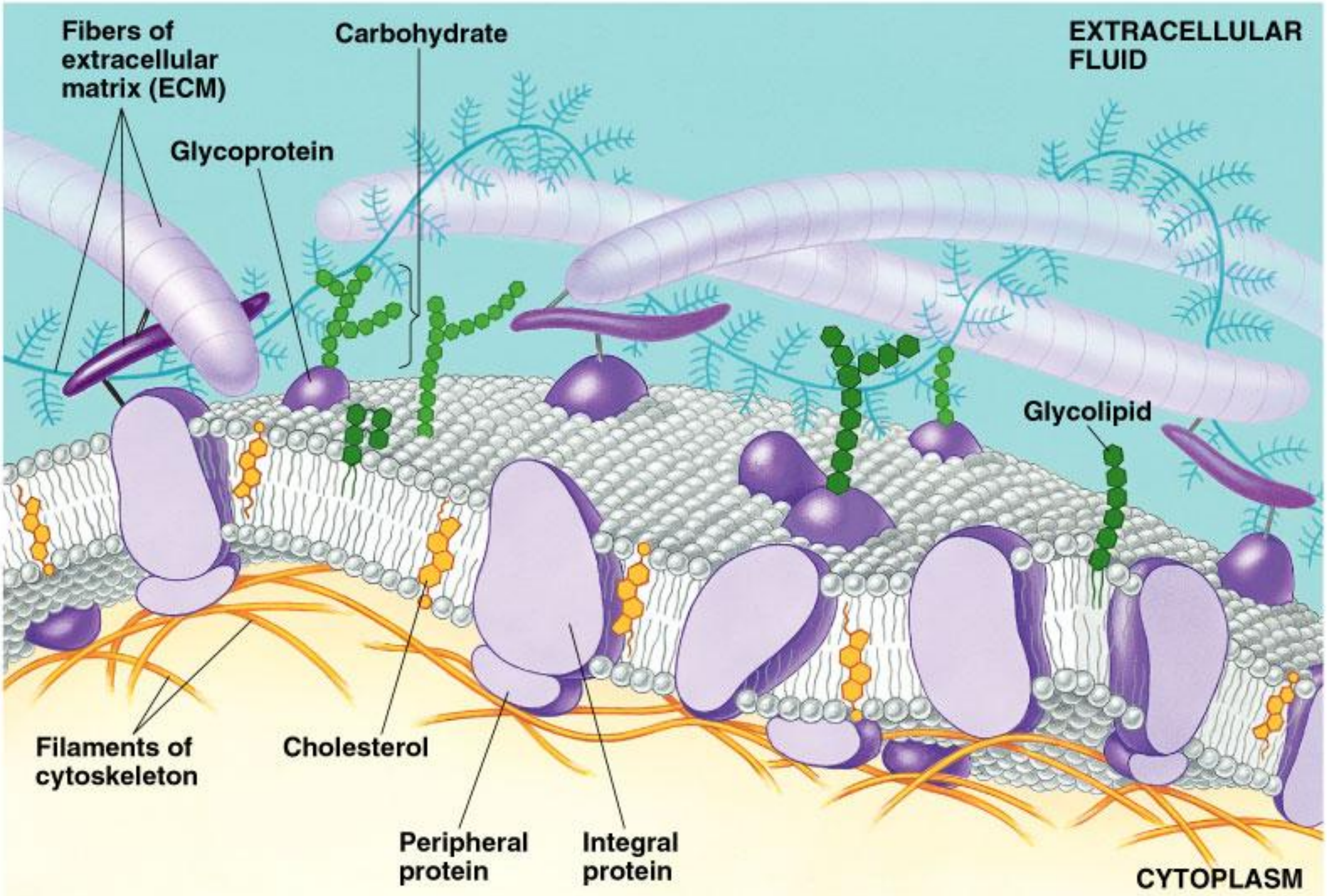


Arachidonic Acid
(all-cis-5,8,11,14-eicosatetraenoic acid)

$$\overset{\omega}{CH_3} - (CH_2)_n - \overset{4}{CH_2} - \overset{\beta}{\overset{3}{CH_2}} - \overset{\alpha}{\overset{2}{CH_2}} - \overset{1}{COOH}$$






Fibers of extracellular matrix (ECM)
Carbohydrate
EXTRACELLULAR FLUID
Glycoprotein
Glycolipid
Filaments of cytoskeleton
Cholesterol
Peripheral protein
Integral protein
CYTOPLASM

The digestion and absorption of fats

The beginning: in the mouth by the lipases produced by the glands of tounge. They are still active in the stomach.

Fats are not water soluble $\rightarrow$ **slow process**

$\downarrow$

bile acids

Digestion in the gut (duodenum, jejunum)

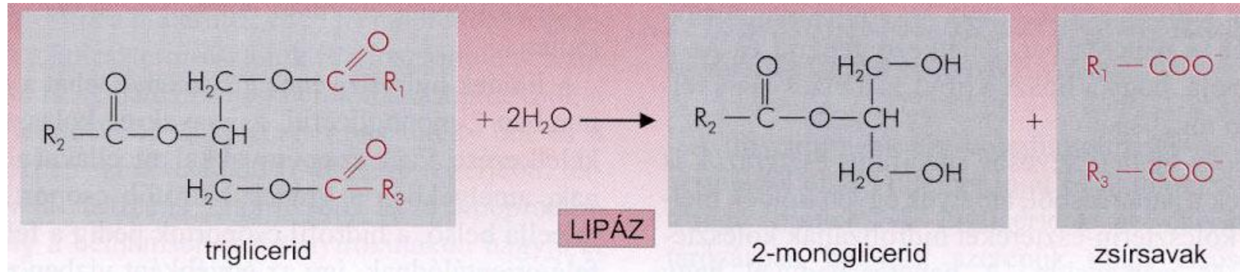
Ingestion (protein, fat) $\rightarrow$ **cholecystokinin, secretin**

$\downarrow$

lipase, esterases

Pancrteatic lipase

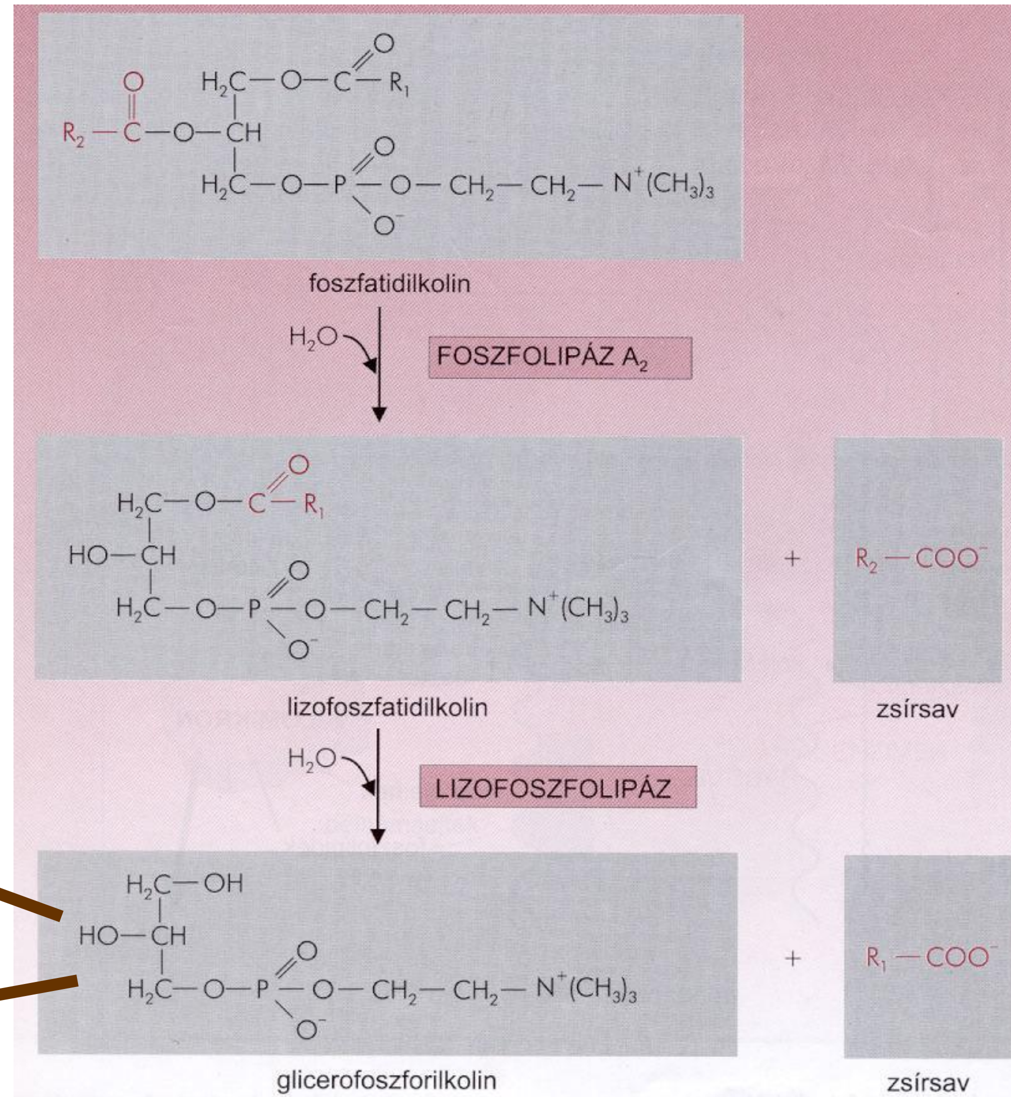
Colipase



Secretum of pancrease: phospholipase A_2 proenzyme

trypsine

active phospholipase A_2



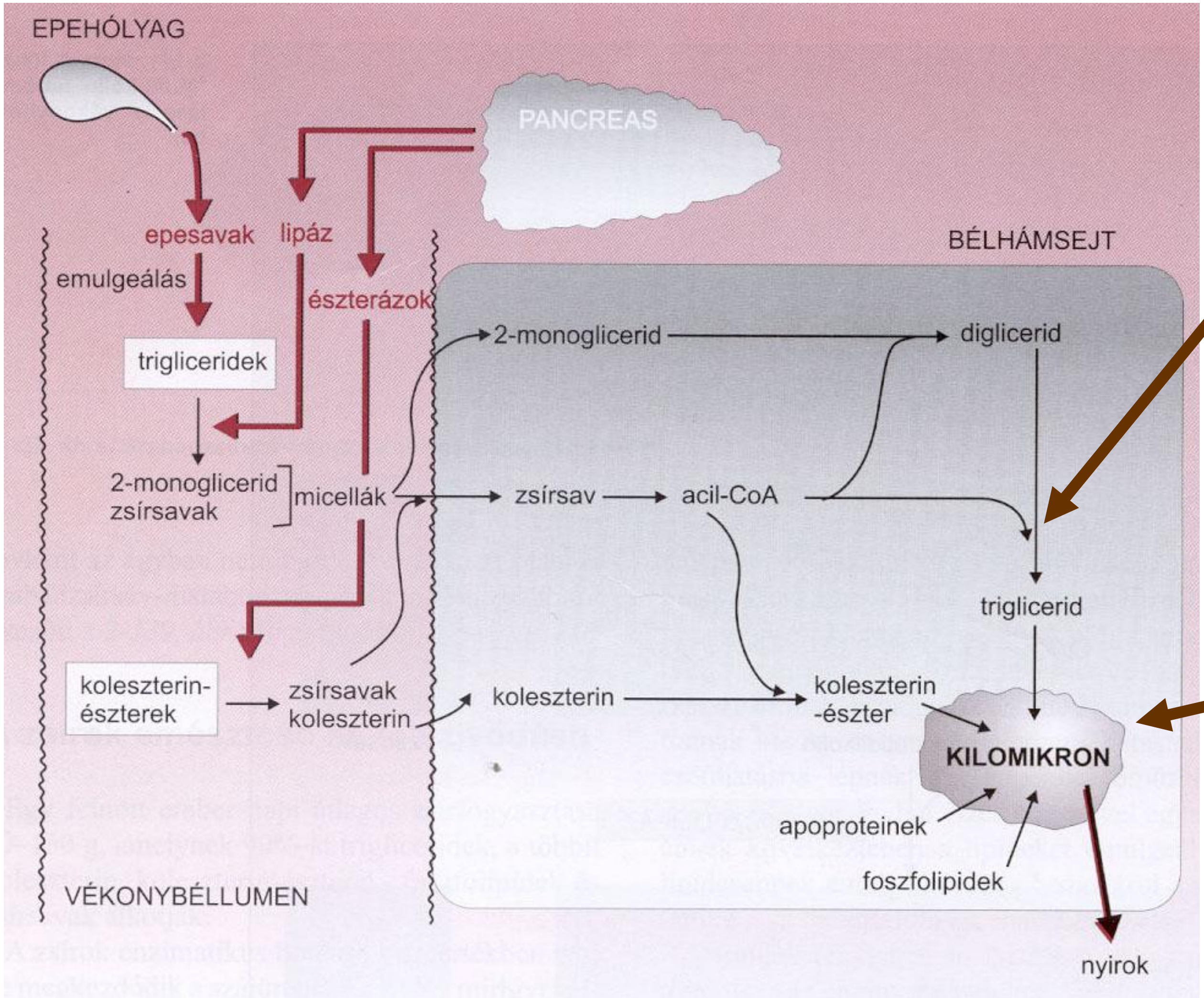
Lisophospholipase: the hidrolysis of the other fatty acid

széklet

További bontás után felszívódik

Endproducts: 2-monoglycerid, fatty acids, cholesterol

Micelle formation together with bile acids



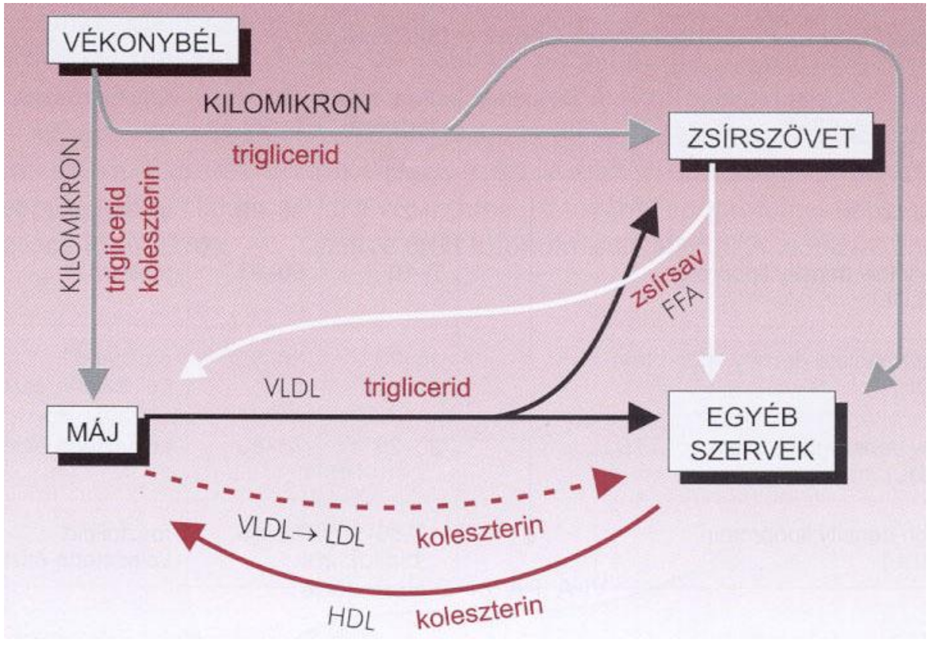
Triglycerid resynthesis

Chylomicron formation

Transport of lipids, lipoproteins

A táplálék lipidjeinek el kell jutni a felhsználó szövetekhez és a májhoz. A plazma vizes közegében nem oldódnak

Most hydrofobic molecules: fatty acids, triglycerols, cholesterol, choleszterol-esthers



Diffetrens transport strategies:

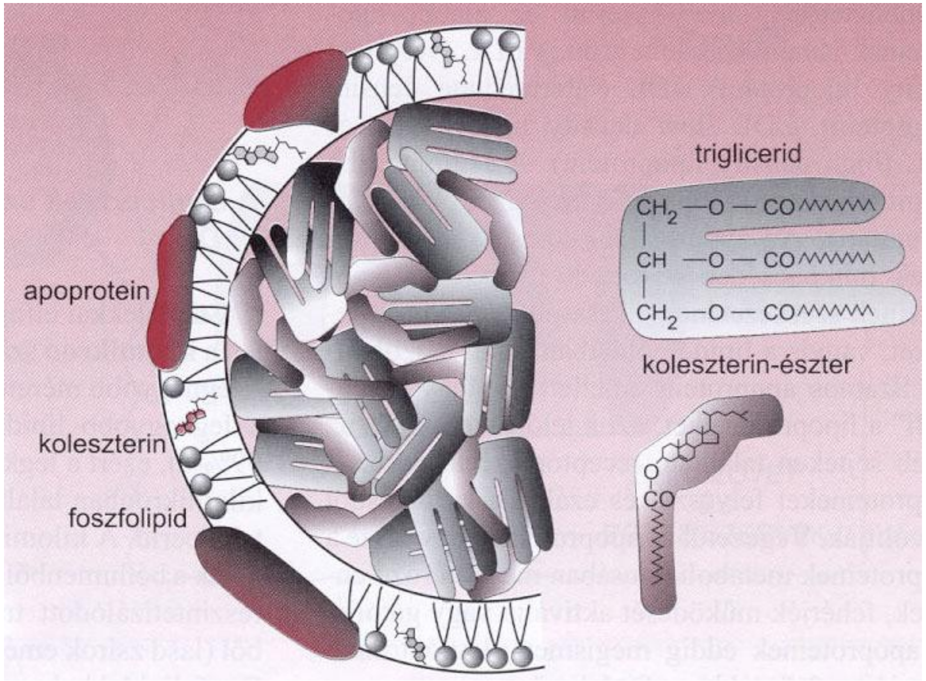
1. **Fatty acids: bind to albumin**

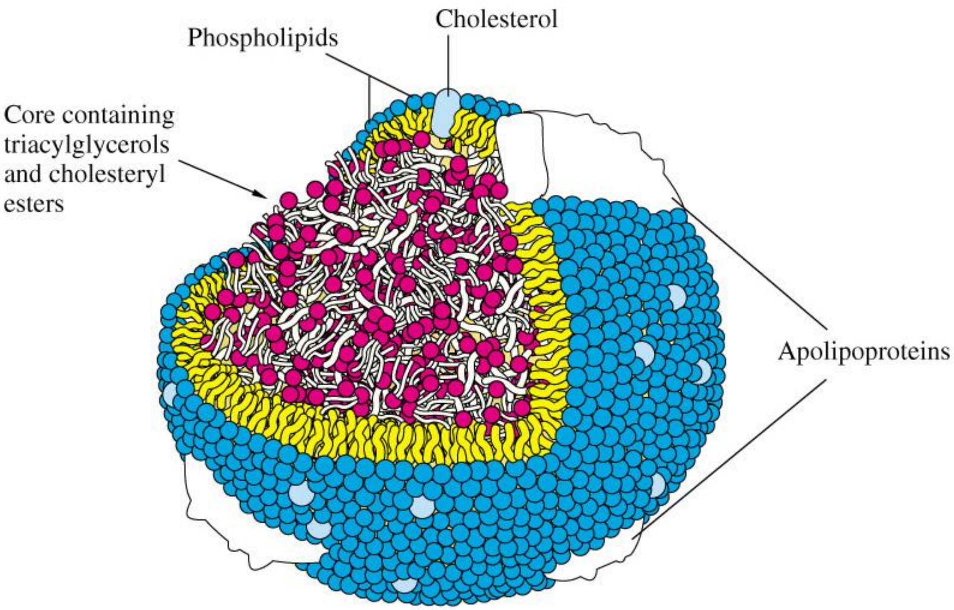
2. triglycerols, cholesterol, cholesterol-esthers : transported by lipoproteins

Lipoproteins: hydrophilic shell hidrofób lipidek számára

Apoproteins: protein components of the hydrophobic shell

Phospholipids: the (amphiphatic) lipid components of the shell





Cholesterol can be found in the shell too.

The core of lipoproteins: triglycerols, cholesterol, cholesterol-esthers.

This stucture is a general feature of all lipoproteins

However their contents are different: different protein, lipid content/ratio

They have different density

They can be separated by ultracentrifugation or by electrophoretic techniques

Lipoprotein	Denzitás	Fehérje-tartalom (%)	Lipid-tartalom (%)	Legfontosabb lipid	Legfontosabb apoprotein
kilomikron		1–2	98–99	triglicerid	B 48, C-II, C-III, E
very low density lipoprotein (VLDL)		7–10	90–93	triglicerid	B-100, C-I, C-II, C-III, E
intermediate density lipoprotein (IDL)		15–20	80–85	triglicerid koleszterin-észter	B-100, E
low density lipoprotein (LDL)		20–25	75–80	koleszterin-észter	B-100
high density lipoprotein (HDL)		40–55	50–55	foszfolipid koleszterin-észter	A-I, A-II, C-I, C-II, C-III, E

The roles of apoproteins

- structural roles (skeleton of lipoproteins),

- surface markers, LPs are recognized by the cells on the base of APs

- They are activators and inhibitors of important enzymes in lipid metabolism

Apoprotein	Funkció
A-I	aktiválja a LCAT enzimet
B-100	kötődik az LDL-receptorhoz
C-II	aktiválja a lipoprotein-lipázt
C-III	gátolja a VLDL felvételét a májban
E	elősegíti a kilomikron remnant felvételét a májban

Chylomicron:

- The transport of ingested lipids from the intestine

- high lipid/protein ratio (98-99 % of dry weight) → lowest density

- It forms in the intestinal epithel from resynthesized triglycerols, cholesterol

- apoproteins are added to the lipid micelles (apo B-48, A-I, A-IV)

→ Lymph nodes → circulation

Lipoprotein	Denzitás	Fehérje-tartalom (%)	Lipid-tartalom (%)	Legfontosabb lipid	Legfontosabb apoprotein
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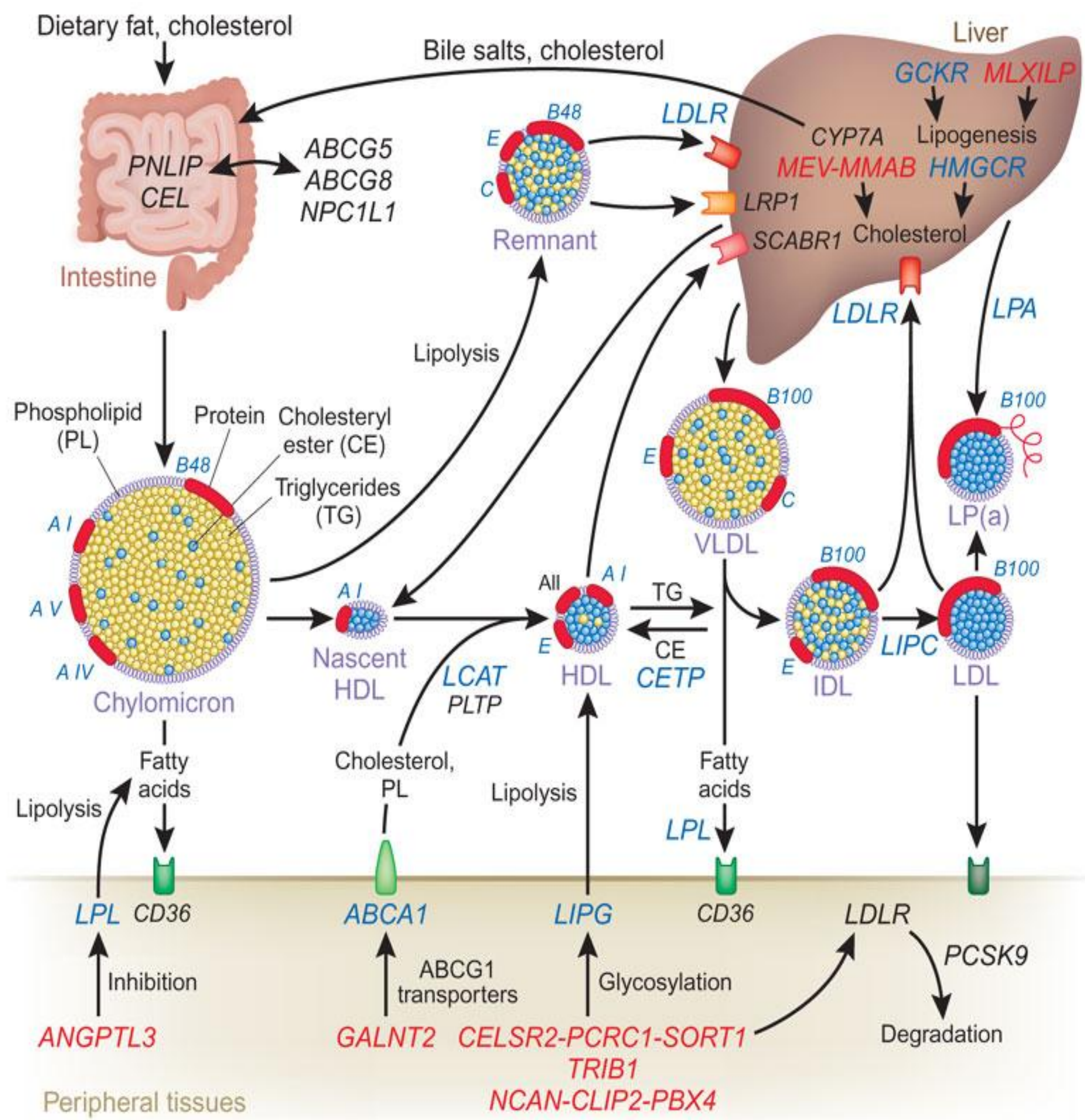
Further apoproteins (apoE, CII, CIII) are added in the circulation

Apoprotein C-II : the cofactor of the enzyme

Adipose tissue, heart muscle, sceletal muscle, lactating breast: lipoprotein lipase (triglycerols are cleaved to glycerol, and fatty acid)

Chylomicron remnant: higher density, lower triglicerol content

It is taken up by liver cells on the base of apo E marker


Dietary fat, cholesterol
Bile salts, cholesterol
Liver
GCKR
MLXILP
Lipogenesis
CYP7A
MEV-MMAB
HMGCR
Cholesterol
LDLR
LRP1
SCABR1
LDLR
LPA
PNLIP
CEL
ABCG5
ABCG8
NPC1L1
Intestine
B48
E
C
Remnant
Lipolysis
Phospholipid
(PL)
Protein
Cholesteryl
ester (CE)
Triglycerides
(TG)
B48
A I
A V
A IV
Chylomicron
A I
Nascent
HDL
LCAT
PLTP
All
A I
E
HDL
TG
CE
CETP
B100
E
C
VLDL
B100
E
IDL
LIPC
B100
LDL
B100
LP(a)
Fatty
acids
Lipolysis
Cholesterol,
PL
Lipolysis
Fatty
acids
LPL
LPL
CD36
ABCA1
LIPG
CD36
LDLR
PCSK9
Degradation
Inhibition
ABCG1
transporters
Glycosylation
ANGPTL3
GALNT2
CELSR2-PCRC1-SORT1
TRIB1
NCAN-CLIP2-PBX4
Peripheral tissues

Lipids from the liver are transported by Very Low Density Lipoprotein (VLDL).

Lipoprotein	Denzitás	Fehérje-tartalom (%)	Lipid-tartalom (%)	Legfontosabb lipid	Legfontosabb apoprotein
kilomikron	↓	1–2	98–99	triglicerid	B 48, C-II, C-III, E
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The sources of fatty acids in triglycerols:

- Chylomicron remnant

- Free fatty acids taken up by the liver

- Fatty acids synthesized by the liver

The sources of cholesterol

meal, biosynthesis

Cholesterol/triglycerol ration in the VLDL: ¼

Cholesterol reach diet: 1/1

Typical apoprotein: B-100

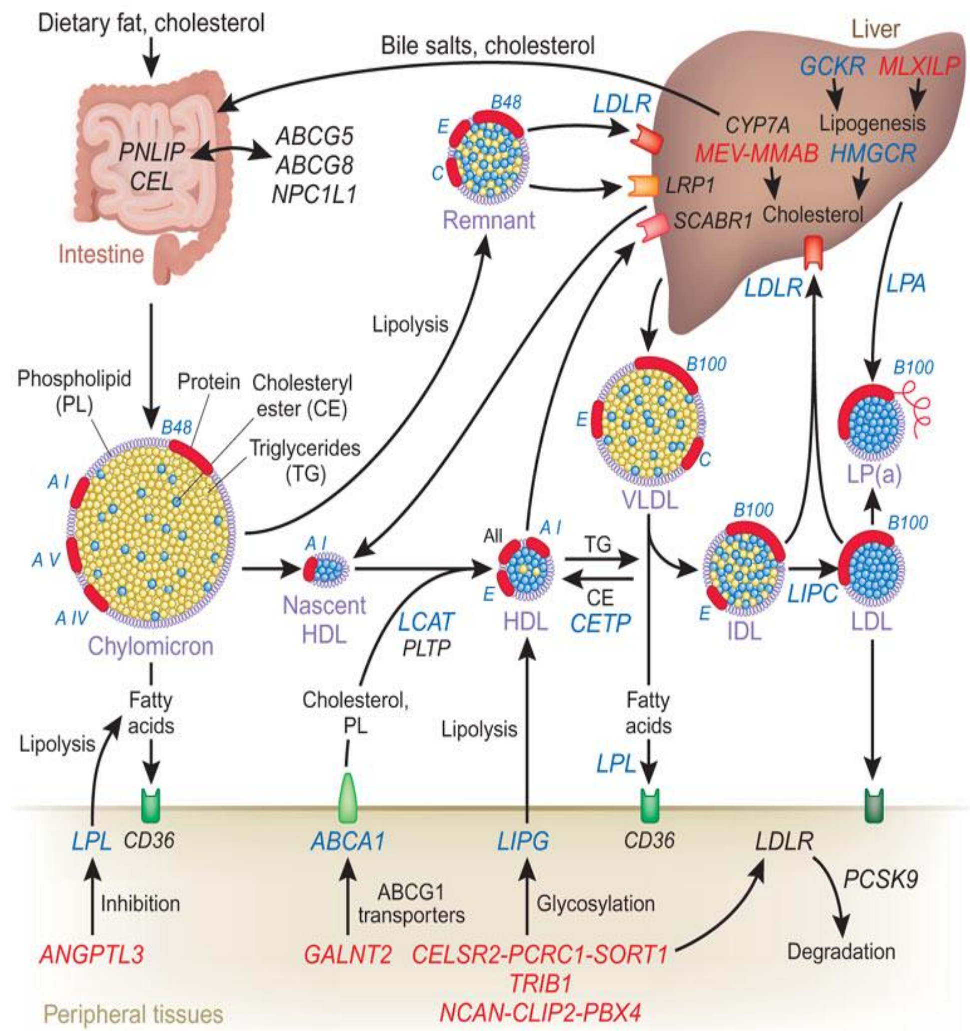
VLDL is transported to the periferial tissues and its triglycerol content is cleaved by the lipoprotein-lipase

IDL

50%

Taken up by the liver cells (apo E)

Remain in the circulation and IDL is converted to LDL



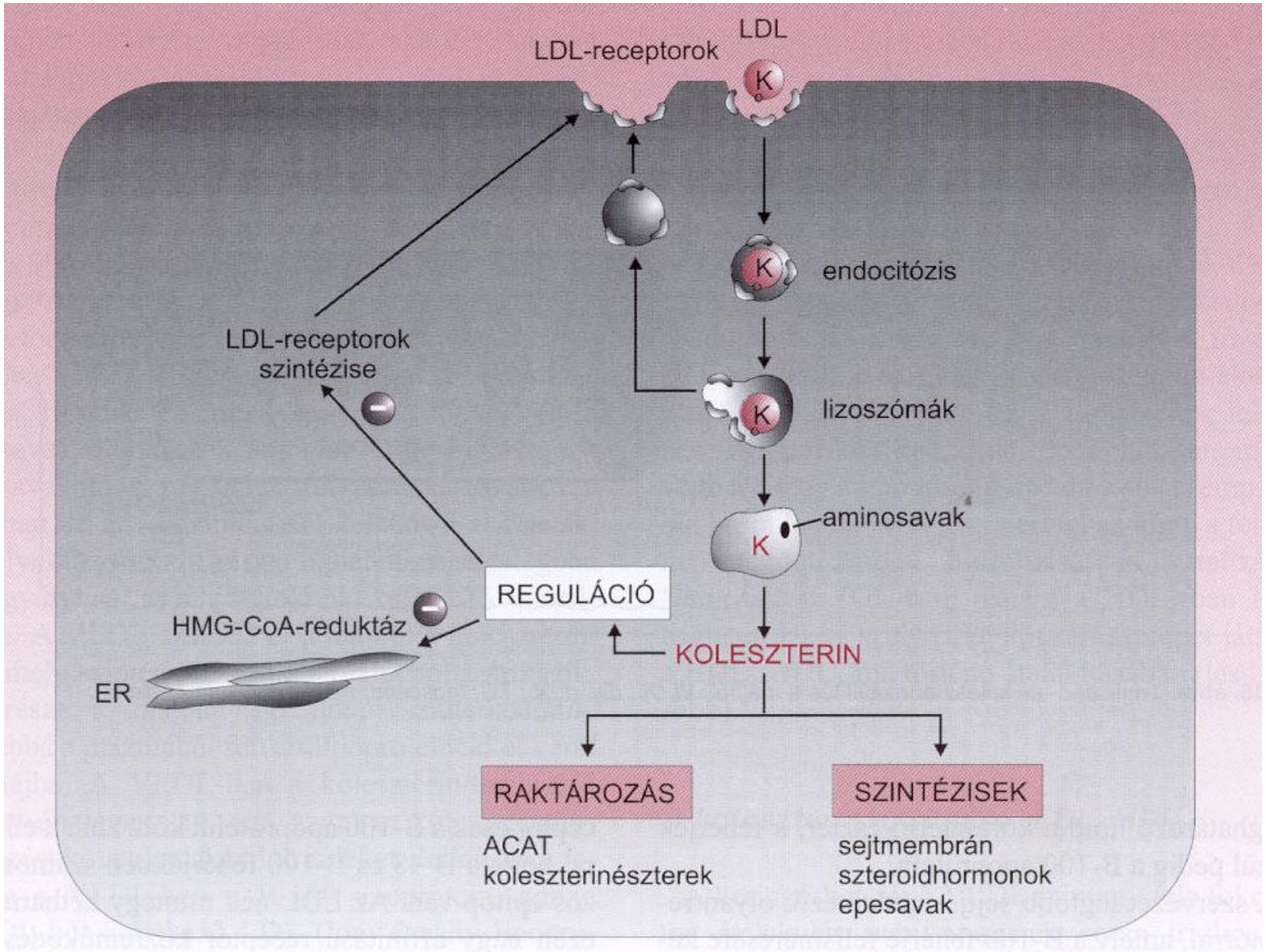
Low Density Lipoprotein: LDL

Typical lipid component: cholestol-esther

Apoprotein: B-100

The 2/3 of LDL leave the circulation through B-100 receptors.

Important organs: liver, intestine, adrenal glands, gonads



Familiar hypercholesterinaemia

The number or the functional deficiency of B-100 receptors can be in the background.

Due to mutations:

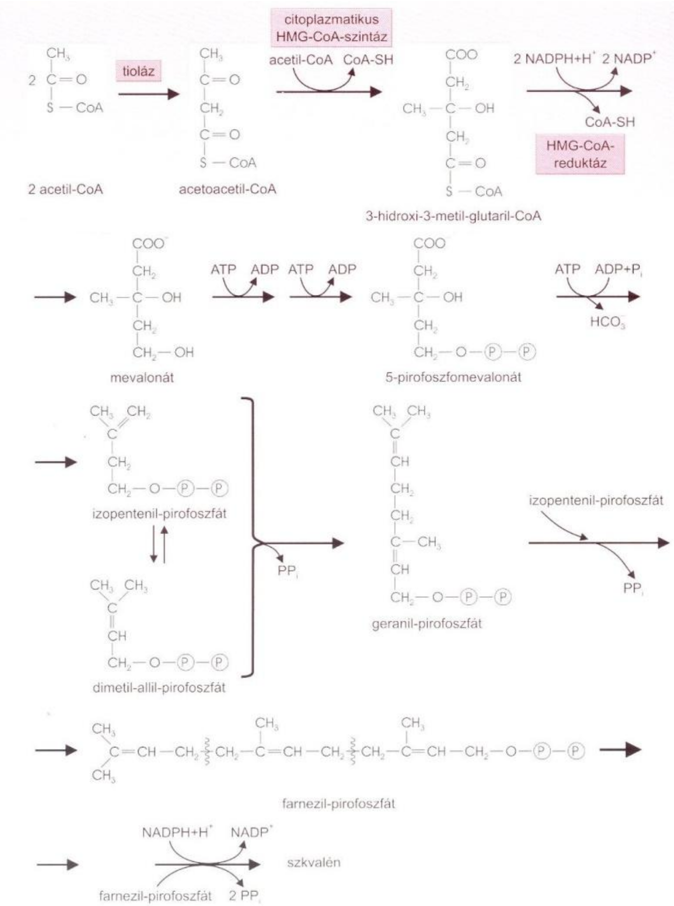
1. Deficiency in receptor synthesis
2. Deficiency in the posttranslational modification
3. Structural changes in the ligand binding domain

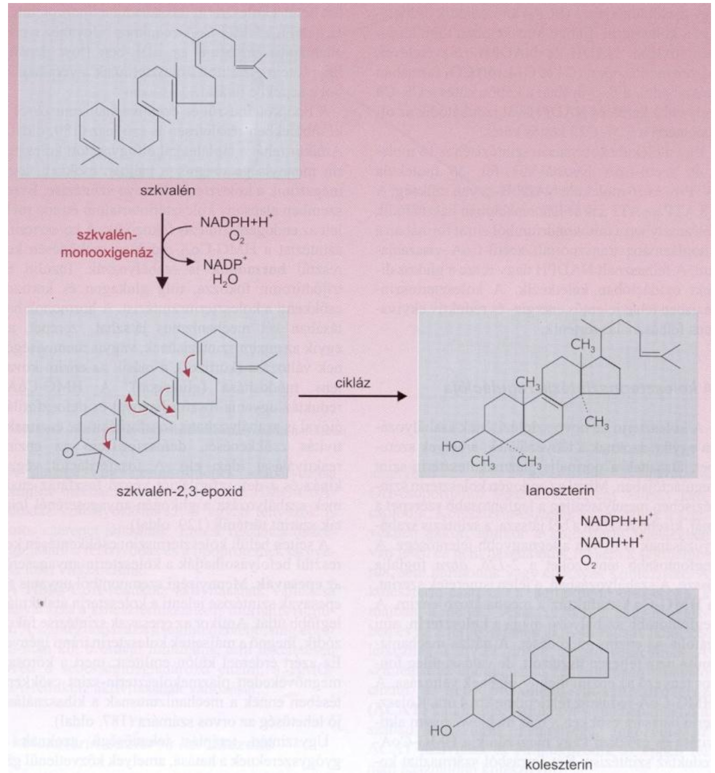
Heterozygotic form: the number of (functional) receptors is the half of wild type

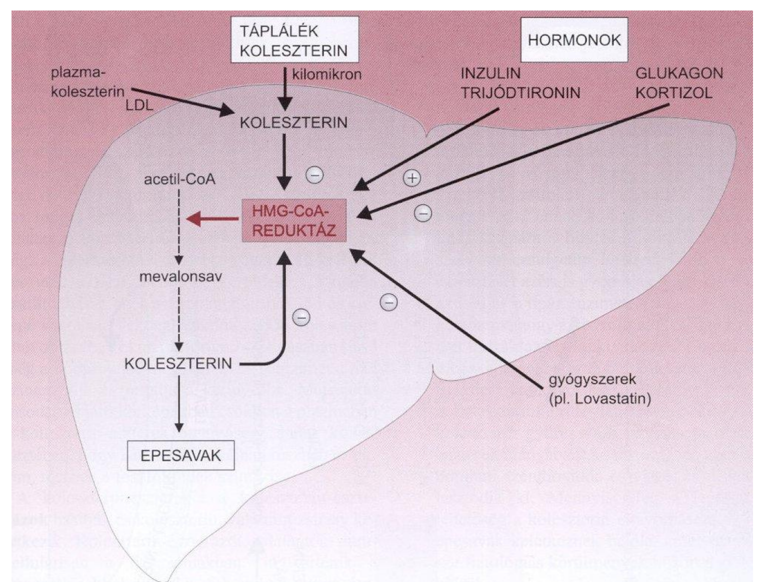
Therapy: the inhibition of cholesterol biosynthesis by statins, or the application of bile acid binding resins

Homozygotic form: total deficiency of receptors

Therapy: liver transplantation







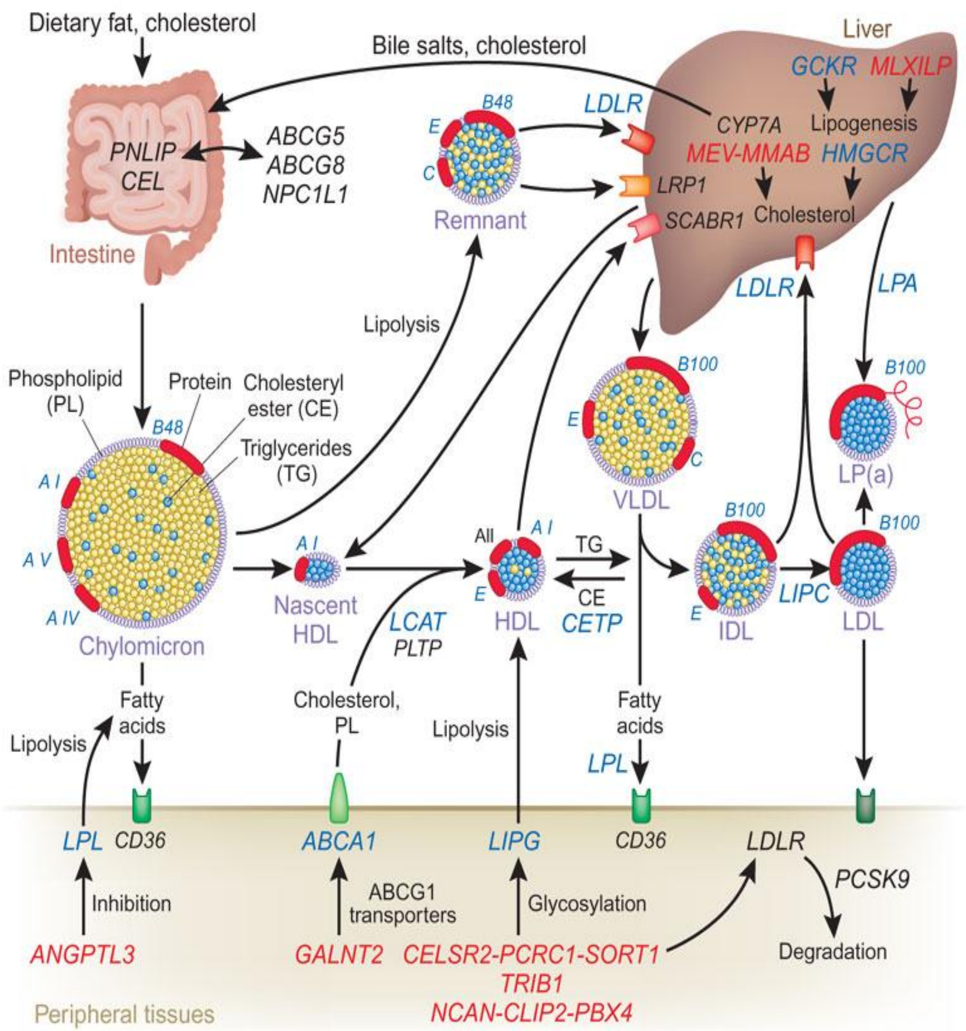
The inhibition of cholesterol biosynthesis via the inhibition of 3-hydroxy-3-methyl CoA reductase by Lovastatin.

High Density Lipoprotein (HDL)

HDL transports cholesterol from the extrahepatic cells and from the artery walls to the liver. „protective or good cholesterol")

Typical apoprotein: apo E.

LCAT: lecithin:cholesterol acyltransferase. This enzyme is responsible for the formation of cholesterol-esthers.



Alternative way of LDL removal: Macrophags take up LDL by the mediation of (scavenger) receptors

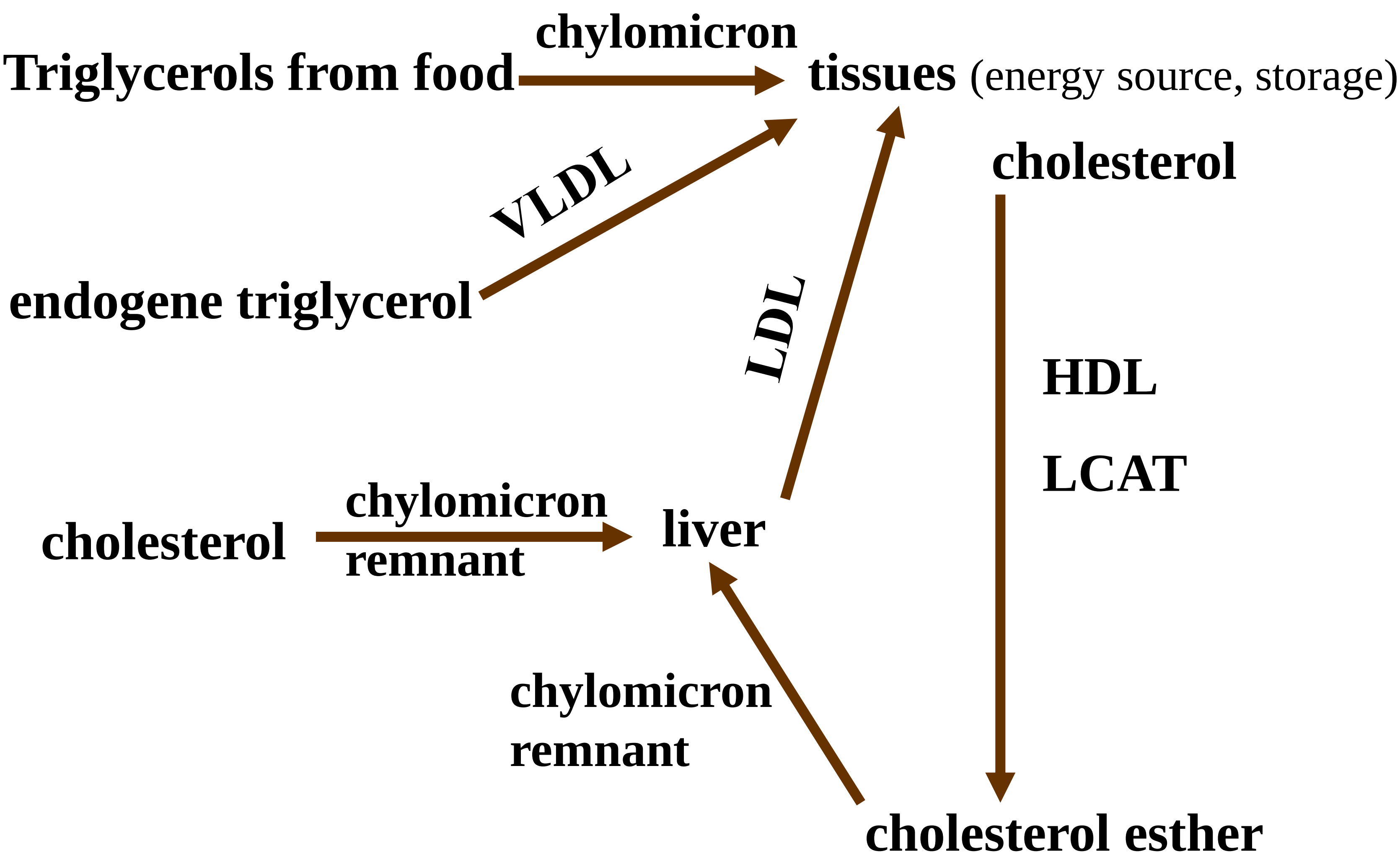
It has higher importance at higher LDL concentration

Saturating by cholesterol-esthers

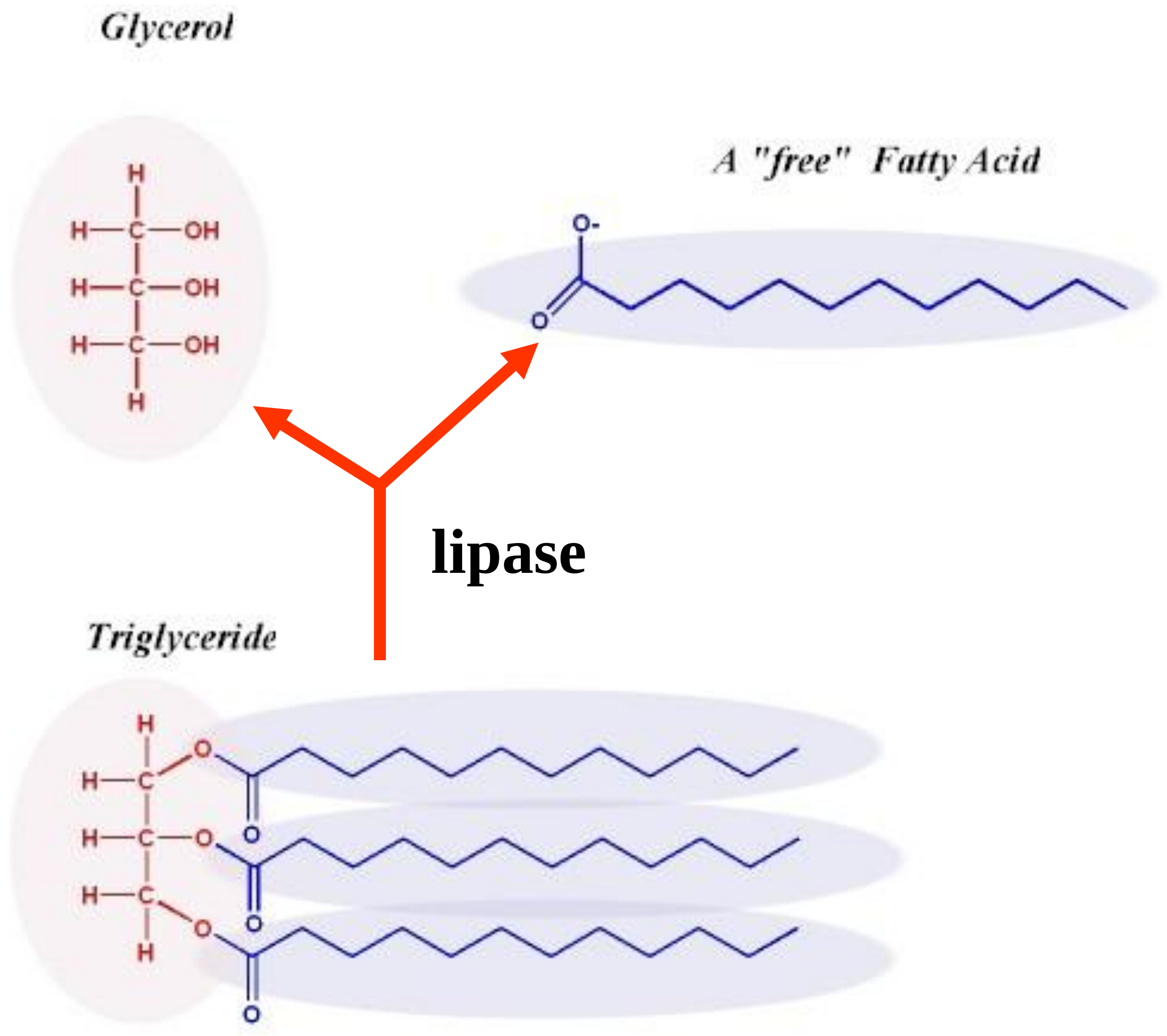
Foam cell

Typical componenet of atherosclerosis plaque

Summary of lipid transport metabolism



Lipolysis: the release of fatty acids from the adipose tissue



The fate of glycerin:

Back to the liver

glycerin $\xrightarrow{\text{glycerin-kinase}}$ **glycerin-3-phosphate**

tryglyceride synthesis **dihydroxi-aceton-phosphate**

glycolysis **gluconeogenesis**

The fate of fatty acids:

They are transported in the blood connected to albumin to the periferial tissues

oxydation → energy

Fatty acid utilization

- **heart muscle**
- **skelatal muscle**

No fatty acid utilization

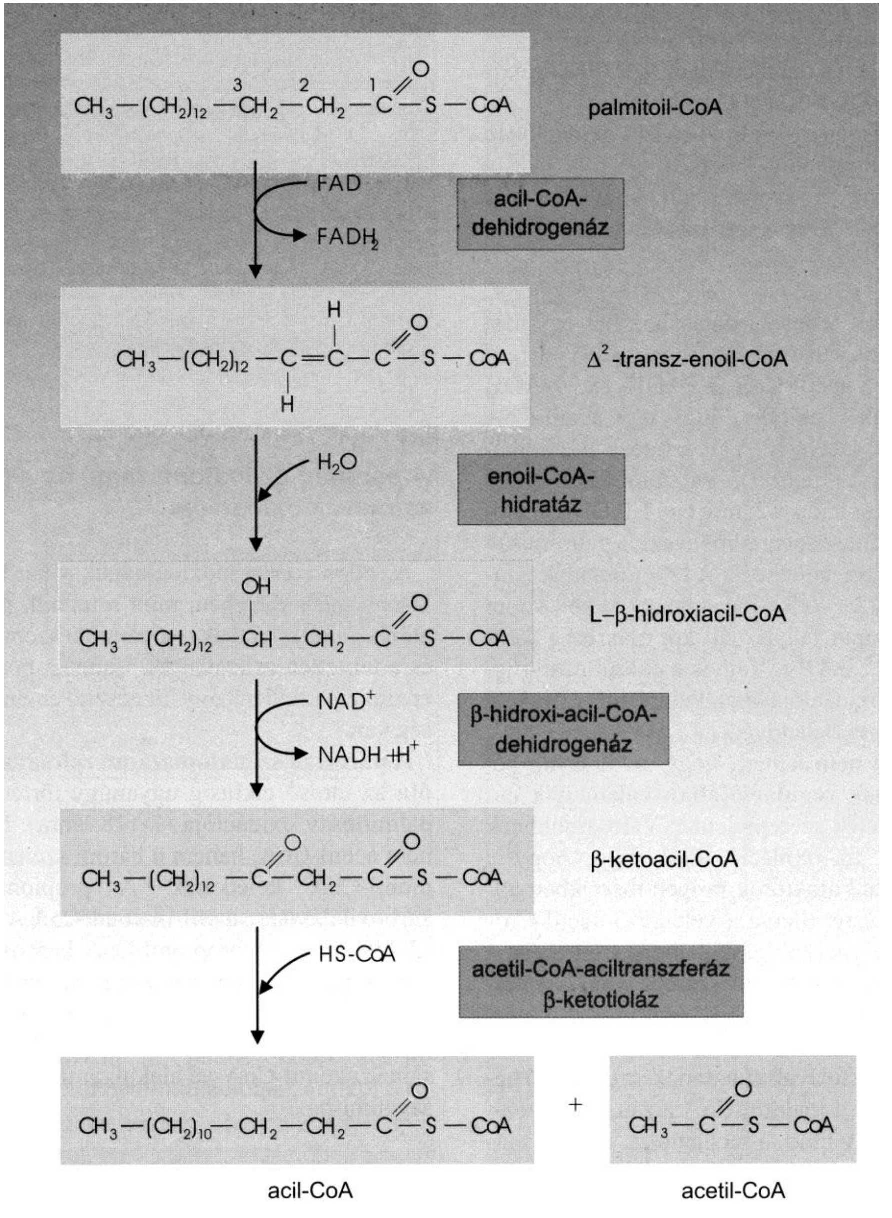
- **nerve tissue**
- **red blood cells**
- **medular cells of adrenal glands**

It depends on the food intake too.

Sated: carbohydrate utilization and storage no fatty acid oxidation → fatty acid synthesis

Starvation, physical activity: fatty acid oxidation

The β-oxidation of fatty acids



1. oxidation: $FADH_2$, double bond in trans position

2. Hydratation: β-hydroxi fatty acid in L-configuration

3. The oxidation of OH group on the β-carbon

4. tiolysis

Products of every cycle: shorter (2 carbon) fatty acids, 1 acetyl-CoA, 1 $FADH_2$, 1 NADH

Citrate cycle

$FADH_2$,NADH

Terminal oxidation

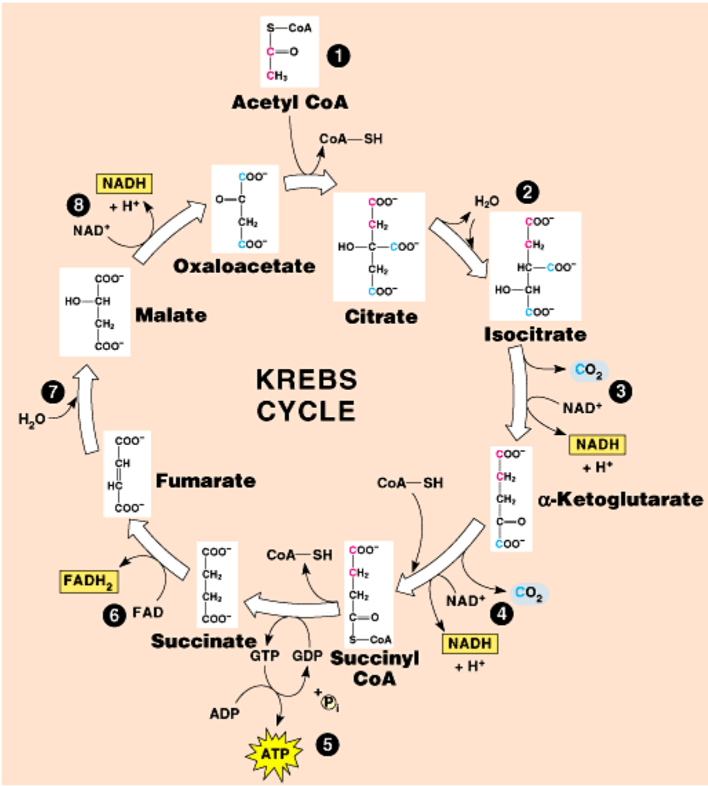
ENERGY

Catabolism of 1 palmytic acid (16 C-atom):

- **7 cycles**
- **8 acetyl-CoA**
- **7 FADH2**
- **7 NADH**

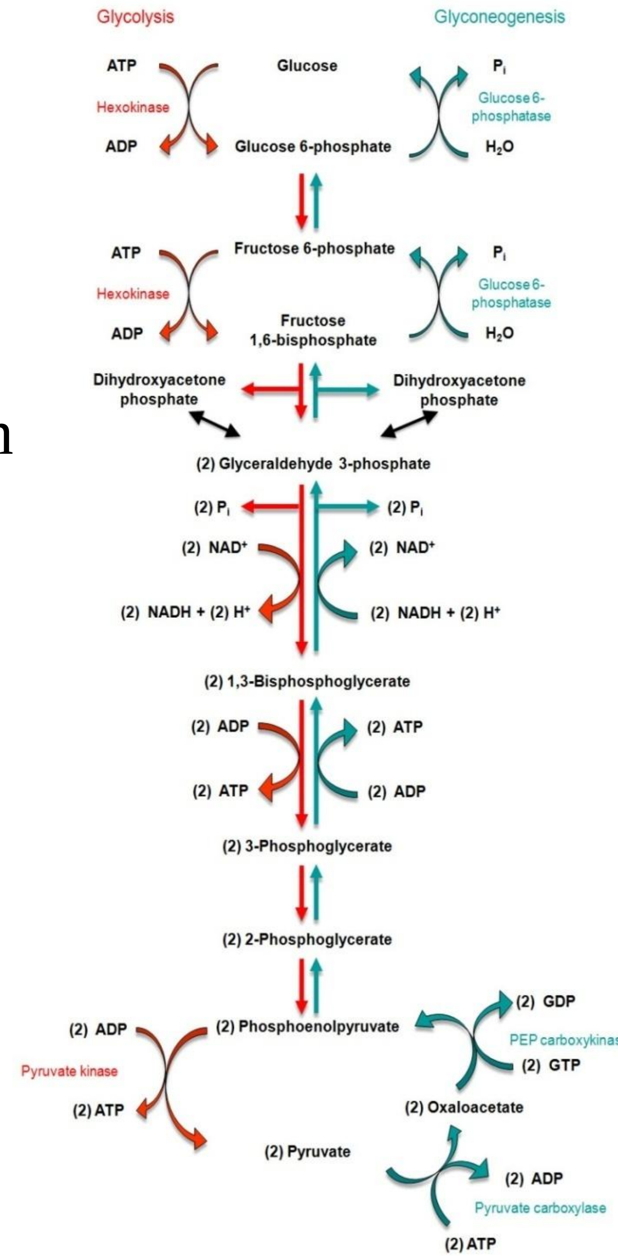
Netto: 129 ATP

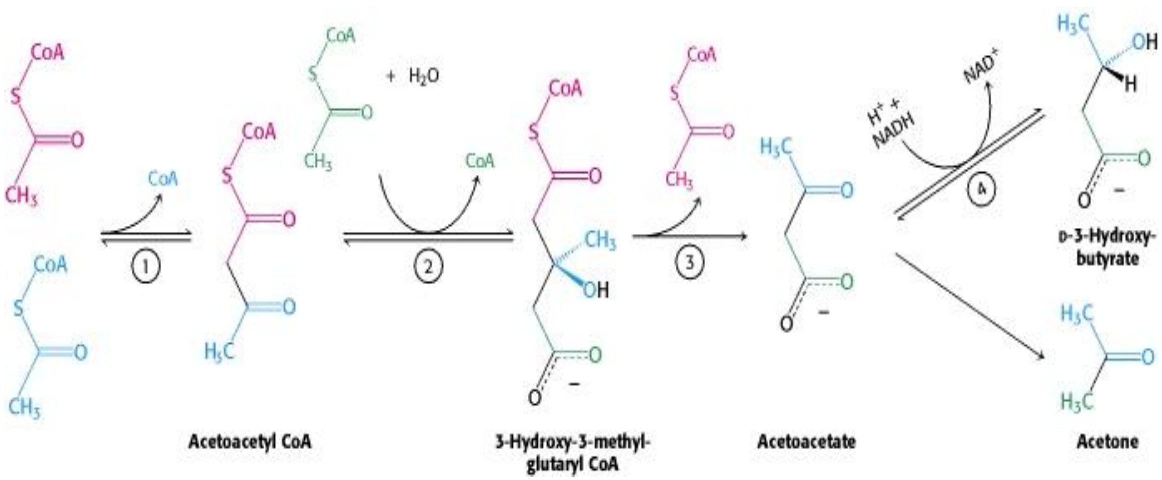
Formation of ketone bodies



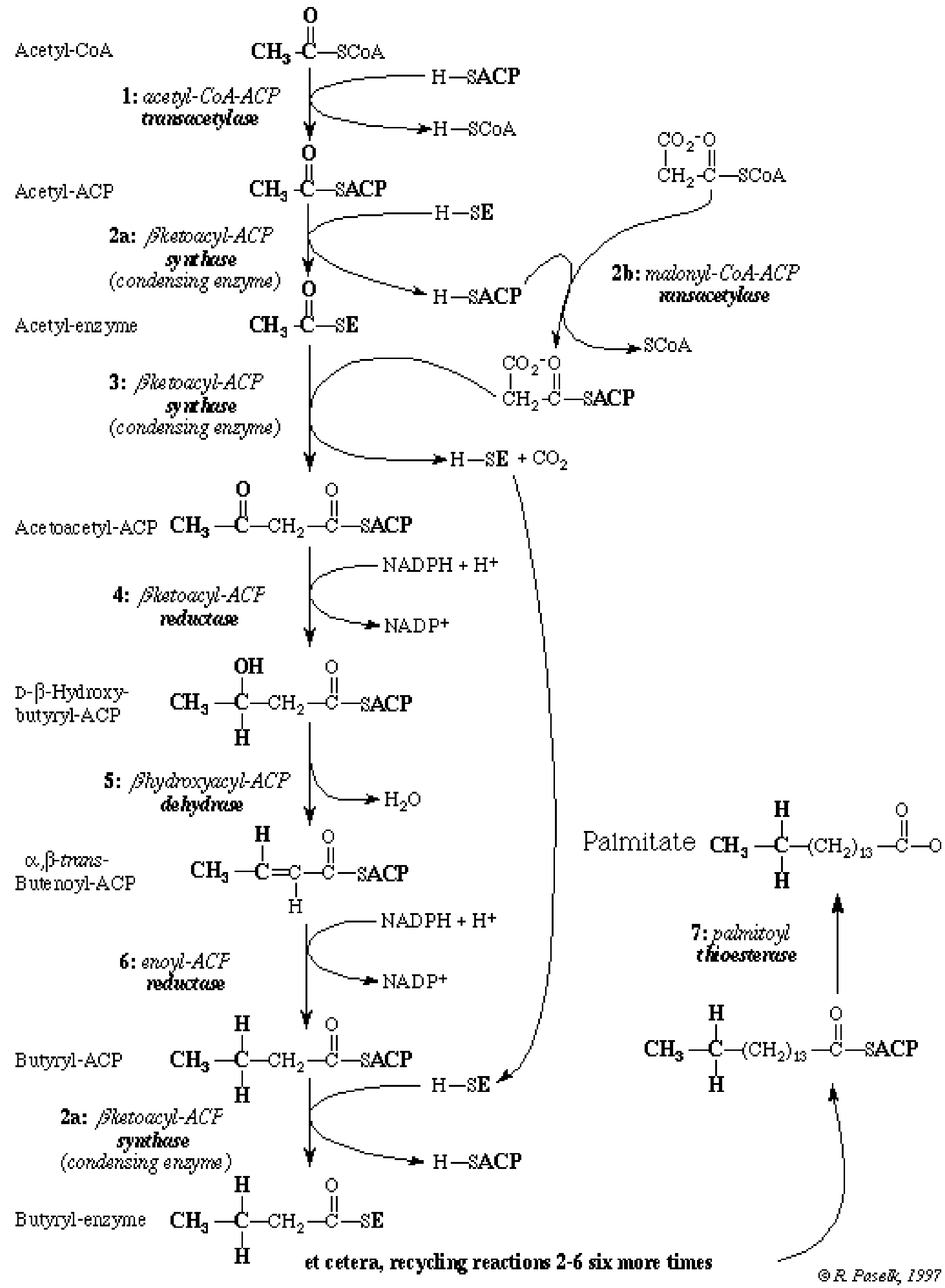
The concentration of oxaloacetate is limited in the mitochondria.

It also consumes in liver cells by the gluconeogenesis





Biosynthesis of fatty acids



Biosynthesis of cholesterol